Paper No. 20

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte KIM SZE TAN

Appeal No. 2001-1727
Application No. 08/425,682

ON BRIEF

Before ADAMS, MILLS and GRIMES, Administrative Patent Judges.

MILLS, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 10-25 which are the claims pending in this application.

Claim 10 is representative of the claims on appeal and reads as follows:

10. A humanised monoclonal antibody, or antigen-binding fragment thereof, comprising regions of antibodies from different animal species, wherein a hypervariable region of the variable region of said humanised antibody comprises a hypervariable region from a high-affinity non-rodent, non-human monoclonal antibody, wherein said high-affinity non-rodent, non-human monoclonal antibody has an antigen binding affinity of at least about 10^{11} 1/mol, and wherein a variable framework region of said variable region of said humanised monoclonal antibody comprises a human immunoglobulin variable framework region and wherein a constant region of said humanised monoclonal antibody comprises, human immunoglobulin constant region.

The references relied upon by the examiner are:

Morrison, S.L. (Morrison), "Transfectomas Provide Novel Chimeric antibodies," Science, Vol. 229, pp. 1202-1207 (1985)

Queen, C. et al. (Queen), "A humanized antibody that binds to the interleukin 2 receptor," Proc. Nat. Acad. Sci., Vol. 86, pp. 10029-10033 (1989)

Groves, D.J. et al. (Groves 1), "Production of an Ovine Monoclonal Antibody to Testosterone by an Interspecies Fusion," Hybridoma, Vol. 6, No. 1, pp. 71-76 (1987)

Groves, D.J. et al. (Groves 2), "The preparation of ovine monoclonal antibody to progesterone," Journal of Endocrinology, Vol. 126, pp. 217-222 (1990)

Steward, M.W. et al. (Steward), "Antibody Affinity: Thermodynamic Aspects and Biological Significance," CRC Press, Inc., pp. 145-153 (1983)

Sevier, E.D., et al. (Sevier), "Monoclonal Antibodies in Clinical Immunology," Clinical Chemistry, Vol. 27, No. 11, pp. 1797-1806 (1981)

Rainey, P. M. (Rainey), "Effects of Digoxin Immune Fab (ovine) on Digoxin Immunoassays," American J. of Clinical Pathology, Vol. 92, No. 6, pp. 779-786 (1989)

Ehrlich, P. H. (Ehrlich), "Human and Primate Monoclonal Antibodies for in Vivo Therapy," Clinical Chemistry, Vol. 34, No. 9, pp. 1681-1688 (1983)

Grounds of Rejection

Claims 10-25 stand rejected under 35 U.S.C. § 103(a) as obvious over Morrision and Queen taken with Groves 1, Groves 2, Steward, Sevier, Rainey and Ehrlich.

We reverse.

DISCUSSION

In reaching our decision in this appeal, we have given careful consideration to the appellant's specification and claims, to the applied prior art references, and to the respective positions articulated by the appellant and the examiner.

Rather than reiterate the conflicting viewpoints advanced by the examiner and the appellant regarding the above-noted rejection, we make reference to the Examiner's Answer for the examiner's complete reasoning in support of the rejection, and to the appellant's Brief for the appellant's arguments thereagainst. As a consequence of our review, we make the determinations which follow.

35 U.S.C. § 103

Claims 10-25 stand rejected under 35 U.S.C. § 103(a) as obvious over Morrison and Queen taken with Groves 1, Groves 2, Steward, Sevier, Rainey and Ehrlich.

In rejecting claims under 35 U.S.C. § 103, the examiner bears the initial burden of presenting a prima facie case of obviousness. See In re Rijckaert, 9 F.3d 1531, 1532, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993). A prima facie case of obviousness is

established when the teachings from the prior art itself would appear to have suggested the claimed subject matter to a person of ordinary skill in the art. In re Bell, 991 F.2d 781, 783, 26 USPQ2d 1529, 1531 (Fed. Cir. 1993). An obviousness analysis requires that the prior art both suggest the claimed subject matter and reveal a reasonable expectation of success to one reasonably skilled in the art. In re Vaeck, 947 F.2d 488, 493, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991). Both the suggestion and the reasonable expectation of success must be found in the prior art, not in appellant's disclosure. In re Dow Chem. Co., 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). With this as background, we analyze the prior art applied by the examiner in the rejection of the claims on appeal.

The examiner indicates that both Morrison and Queen teach general methods for producing chimeric and humanized antibodies. Answer, page 4. These references provide motivation for administering chimeric and humanized antibodies as opposed to non-human antibodies in order to reduce adverse immunological reactions in human recipients. Answer, pages 4-5.

Queen and Morrison are found by the examiner to differ from the instant invention in that they do not specifically teach humanized or chimeric antibodies having non-rodent variable regions with binding affinities of at least 10^{11}. Answer, page 5. The examiner thus relies on each of the Groves references for teaching methods for generating high affinity ovine monoclonal antibodies. Steward is relied on by the

examiner for the teaching that the art recognized that high antibody affinity is superior to lower antibody affinity in terms of mediating a number of biological reactions. Answer, page 6. Sevier is relied on for its general disclosure of the advantages in the art of using monoclonal antibodies as compared to polyclonal antibodies. Id. Rainey teaches that the administration of ovine antidigoxin Fab was an established therapy for humans suffering from digitalis toxicity. Ehrlich teaches that the use of sheep anti-digoxin Fab is limited to life-threatening situations due to the adverse immunological reactions associated with their administration. Id.

The examiner summarizes (Answer, pages 6-7):

> It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use the methods of Queen et al. or Morrison to produce high affinity, non-rodent (such as ovine) humanized or chimeric antibodies for therapeutic application with a reasonable expectation of success given the art known production of high affinity non-rodent monoclonal antibodies taught by the Groves et al. references and the art-known general applicability of the methods taught by Queen et al. and Morrison to reduce immunogenicity. Further, one of ordinary skill in the art would have been motivated to do so in order to obtain the known advantages of high affinity antibodies in clinical applications as taught by Steward et al. and the reduction of harmful, clinical immune responses associated with the clinical administration of non-rodent antibodies as taught by Erhlich et al.

Appellant argues that the examiner has failed to provide sufficient evidence to support a prima facie case of obviousness. In particular, appellant argues (Brief, page 12):

> ... the Queen *et al.* and Morrison references, do not mention or suggest the possibility of preparing humanized antibodies using non-rodent derived monoclonal antibodies as the starting material. The Queen *et al.* reference is specifically directed to the production of a specific mouse antibody that has been humanized and that binds to the interleukin-2 receptor. ... Nor does Morrison teach or suggest the use of antibodies from an animal other than rodents. Applicant respectfully asserts that the Examiner's attempt to characterize Morrison as referring to combinations between species that are not limited to murine and human over generalizes the scope and context of the teachings in the Morrison reference. A fair reading of the Morrison reference shows that the focus and concern was clearly directed towards combinations of rodent and human antibodies, and not to combinations of non-rodent antibodies with human antibodies.

We agree with appellant that the examiner has not met his burden of showing prima facie obviousness as the cited references do not provide sufficient evidence of a reasonable expectation of success. In particular, we find insufficient evidence of record to support a reasonable expectation of success on the part of one of ordinary skill in the art at the time of the present invention to obtain a humanized monoclonal antibody, as claimed, having a non-rodent portion and an antigen binding affinity of at least about 10^{11} l/mol.

In our view, at best the cited references recognize the advantages of preparing humanized antibodies and suggest that non-rodent antibodies, such as ovine antibodies, may have a higher affinity than murine antibodies. Groves 2, page 221, column 2. We do not find however that the cited references provide the requisite expectation of success of obtaining a non-rodent antibody with an affinity of at least about 10^{11} l/mol, as claimed. While Groves 1 describes an ovine monoclonal antibody

to testosterone having an affinity K_D of 7.63 x 10^{-12} mol/l, the non-rodent antibodies such as the human or primate monoclonal antibodies to digoxin described by Ehrlich have an affinity of 3 x10^{10} l/mol, while the ovine monoclonal antibodies to digoxin described by Rainey have dissociation constants centered around 10^{-9}-10^{-10} mol/l. Ehrlich, page 1683, column 2; Rainey, page 783, column 1. The cited art would reasonably appear to indicate that non-rodent antibody affinity is dependent upon various factors, such as the nature of the antigen to which the antibody is raised and the structure of the variable region of the antibody. See, e.g., Queen, page 10033, column 1. The cited references, in our view, indicate a level of unpredictability in the art having particular bearing on the expectation of success of obtaining a non-rodent antibody with an affinity of at least about 10^{11} 1/mol, as claimed.

"In proceedings before the Patent and Trademark Office, the Examiner bears the burden of establishing a prima facie case of obviousness based upon the prior art. '[The Examiner] can satisfy this burden only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references.'" In re Fritch, 972 F.2d 1260, 1265, 23 USPQ2d 1780, 1783 (Fed. Cir. 1992) (citations omitted).

To summarize, the examiner essentially argues that it would have been obvious to try the substitution of the ovine Fab antibody fragment of Groves for the murine variable region in the humanized monoclonal antibodies of Queen or Morrison to obtain

a high affinity antibody. However, "obvious to try" has long been held not to constitute obviousness. In re O'Farrell, 853 F.2d 894, 903, 7 USPQ2d 1673, 1680-81 (Fed. Cir. 1988). A general incentive, as indicated by the examiner, does not make obvious a particular result, nor does the existence of techniques by which those efforts can be carried out. In re Deuel, 51 F.3d 1552,1559, 34 USPQ2d 1210, 1215-16 (Fed. Cir. 1995).

We find it unnecessary to reach additional rebuttal evidence of appellant, the Declaration under 37 C.F.R. 1.132 of Dr. Tan, as we find the examiner has not met the burden of setting forth a prima facie case of unpatentability based on obviousness. In re Oetiker, 977 F.2d 1443, 1446, 24 USPQ2d 1443, 1445 (Fed. Cir. 1992), In re Geiger, 815 F.2d 686, 688, 2 USPQ2d 1276, 1278 (Fed. Cir. 1987).

After argument is submitted by the applicant in response to an obviousness rejection, "patentability is determined on the totality of the record, by a preponderance of evidence with due consideration to persuasiveness of the argument." In re Oetiker, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992); see In re Piasecki, 745 F.2d 1468, 1471-72, 223 USPQ 785, 787 (Fed. Cir. 1984) ("All evidence on the question of obviousness must be considered, both that supporting and that rebutting the prima facie case."). On balance, we believe that the totality of the evidence presented by the examiner and appellant weighs in favor of finding the claimed

invention nonobvious in view of the cited references. The rejection of the claims for obviousness of the claimed invention, is reversed.

CONCLUSION

The rejection of claims 10-25 under 35 U.S.C. § 103(a) as obvious over Morrision and Queen taken with Groves 1, Groves 2, Steward, Sevier, Rainey and Ehrlich is reversed.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a).

REVERSED

DONALD E. ADAMS)
Administrative Patent Judge)
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)
DEMETRA J. MILLS) BOARD OF PATENT
Administrative Patent Judge) APPEALS AND
)
ERIC GRIMES) INTERFERENCES
Administrative Patent Judge)

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